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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,020	12/31/2001	Yuehua Li	5051-451IP	8515

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,020	LI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-11,14-19,24,25,39,42,43,48,50 and 67-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-11,14-19,24,25,39,42,43,48,50 and 67-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-20-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 6-11, 14-19, 24-25, 39, 42-43, 48, 50, and 67-76 are currently pending.

Response to Amendment

2. The Martin Declaration under 37 CFR 1.132 filed 8-20-2004 is insufficient to overcome the rejection of claims 1-4, 7-11, 13-20, 22, 25, 39, 41-43, and 48-50 based upon 35 USC § 112, 1st paragraph, for lack of enablement as set forth in the last Office action because: Applicant's showing was not commensurate in scope with the claimed invention. The Martin Declaration provided evidence that the MANS peptide was capable of inhibiting mucous secretion in animals eliciting mucin hypersecrtion by exposure to ovalbumin and methacholine. The Declaration concludes by stating that they have shown that a peptide directed against the conserved N-terminal region of MARCKS protein inhibits mucin release *in vivo* when instilled intratracheally into allergically inflamed mouse airways. The scope of the MARCKS peptide encompassed by the claimed methods includes those that comprise from 10 to 50 contiguous amino acids from SEQ ID NO: 3, over the entire length of the amino acid sequence of the MARCKS protein, *or* an amino acid sequence (*of unknown length*) comprising an allelic variant comprising deletions or replacements in said sequence. In contrast to the data presented in the Declaration, the peptides encompassed by the claims are not limited to those peptides that are directed against the N-terminal region of the MARCKS protein. The declaration does not provide sufficient evidence that the data presented is predictive or correlative to the behavior of all MARCKS protein fragments directed against the full length sequence of SEQ ID NO: 3.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 6-11, 14-19, 24-25, 39, 42-43, 48, 50, and 67-76 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Written Description), for the reasons of record set forth in the prior Office Action.

The scope of the MARCKS peptides encompassed by the claimed methods includes those that comprise from 10 to 50 contiguous amino acids from SEQ ID NO: 3, over the entire length of the amino acid sequence of the MARCKS protein, *or* an amino acid sequence (*of unknown length*) comprising an allelic variant comprising deletions or replacements in said sequence. According to Applicants "[A]s discussed during the interview, Applicants have enclosed with this response a declaration under 37 C.F.R. § 1.132 from one of the co-inventors, Dr. Linda Martin. This declaration illustrates that an active fragment of a MARCKS protein inhibits mucin release in vivo. Applicants submit that they were in possession of the scope of compounds as presently claimed." Contrary to Applicant's assertions, the Martin Declaration provided only evidence that the MANS peptide functioned to inhibit mucin secretion in animals sensitized with ovalbumin and metacholine. The conclusory statement made by Martin, specifically that "a peptide directed against the conserved N-terminal region of MARCKS protein inhibits mucin release *in vivo,*" does not provide description of the full scope of compound encompassed by the

claims, the claims encompass peptides comprising 10 to 50 contiguous amino acids from allelic variants of SEQ ID NO: 3, or variants comprising deletions of unknown length or sequence.

Applicants were not in possession of the full scope of "active fragments" of all allelic variants of a MARCKS protein that inhibit MARCKS protein-related mucus secretion. At the time of the instant invention, Graff et al. provided evidence that peptides derived from the 25 amino acids comprising the phosphorylation site domain of the MARCKS protein (identical to SEQ ID NO: 2 of the instant application, see page 14391, 1st col.), function to inhibit protein kinase C activity. Protein kinase C is known in the art as an activator of mucus secretion (see Steel et al. described below). Therefore, at the time of the instant invention there was a relationship suggested between PKC regulation of mucus secretion, and the potential for using a MARCKS fragment as an inhibitor of PKC, and an indirect regulator of mucus secretion.

The specification as filed teaches that the MA-PSD peptide functions to increase MARCKS-related mucus secretion when administered to a mucus-secreting cell (see page 9, lines 14-28), and that the MANS-peptide functions to inhibit the release of mucin granules and the secretion of mucus in mucus secreting cells (p. 19, lines 5-14). Both the MANS-peptide and the MA-PSD peptide are both fragments of the MARCKS protein, however the influence of these peptide fragments on MARCK-related mucus secretion is completely opposite. Therefore, simply because Applicants recite that the peptide inhibitors used in the claimed methods comprise from about 10 to about 50 contiguous amino acids from SEQ ID NO: 3, this information is not sufficient to describe functional activity of the peptides used in the claimed methods. The actual functional activity of the peptide must be determined empirically.

It appears that disclosure of the instant application contradicts the findings of Graff et al., see page 9, lines 14-28, which describes the MA-PSD peptide (identical to the peptide of Graff et al.) as an activator, not an inhibitor, of mucus secretion when administered to a mucus-secreting cell (see page 9, lines 14-28). However, it is clear that the specification as filed and the Martin Declaration both provide only evidence of the MANS peptide as an active fragment of the MARCKS protein which functions as an inhibitor of mucus secretion. Moreover, as stated in the prior Office Action, the full scope of compounds useful as inhibitors of MARCKS protein-related mucus secretion must be determined empirically. As per MPEP § 2163[R-1], the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

In the instant case, since it is necessary to perform additional experimentation in order to determine if a putative compound functions to inhibit MARCKS mucus secretion, and furthermore to determine the amount of compound to be administered to a mucus-secreting cell to inhibit mucus secretion in said cell, it is concluded that Applicants were not in possession of the full scope of compounds encompassed by the instant claims. Neither the prior art, nor the specification as filed provides a specific correlation between the structure of the compounds of the present invention and its ability to function to inhibit mucus secretion.

5. Claims 1, 6-11, 14-19, 24-25, 39, 42-43, 48, 50, and 67-76 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting mucus secretion in a cell comprising the administration of the MARCKS derived peptide according to SEQ ID NO: 1, and for stimulating mucus secretion by the administration of the MARCKS derived peptide according to SEQ ID NO: 2 of the instant application, does not reasonably provide enablement for inhibiting mucus secretion in cells by any other peptide besides the peptide according to SEQ ID NO: 1 (MANS peptide), or for using the peptide according to SEQ ID NO: 2 (MA-PSD peptide) for inhibiting mucus secretion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments filed 8-20-04 and 11-30-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by way of amendment, and by asserting that based upon the experimental data provided by the Martin Declaration, particularly wherein the MANS-peptide is shown to be an inhibitor of mucus secretion *in vivo,* and wherein the missense peptide had no effect *in vivo,* the instant rejection should be withdrawn. Contrary to Applicant's assertions, the experimental data set forth in the Martin Declaration, confirms that the specification as filed provided only sufficient guidance for the use of the MANS-peptide to inhibit the release of mucus, and the inability of the specification to enable the use of any fragment of the MARCKS protein in the claimed methods. The Martin Declaration clearly demonstrates the inability of a peptide fragment (RNS) comprising a missense (substitution) mutation to inhibit mucus secretion. The RNS peptide fragment is encompassed by the description of the peptides useful in the claimed methods, however neither the specification as

filed, nor the Martin Declaration provides sufficient guidance for the skilled artisan to use this peptide to inhibit mucus secretion or to treat diseases associated with mucus secretion. Moreover, Applicants asserted that the disease listed in Claim 19 all have a common pathology, as these diseases all affect mucus secretion in the airways of a subject. However, contrary to Applicant's assertions, although these diseases may influence mucus secretion, Applicants have not set forth any particular correlation with treating a symptom associated with these diseases and actually treating the disease condition.

As stated in the prior Office Action, the amount of experimentation required to practice the claimed invention, would require the skilled artisan to resort to de novo experimentation in order to identify other peptide inhibitors or stimulators of MARCKS-related mucus secretion, determining the structure and the pharmacology of the identified peptide inhibitors and peptide stimulators, determining modes of delivery in a whole organism for all categories of peptide inhibitors such that MARCKS-related mucus secretion is inhibited and the desired secondary effect (inhibition or stimulation of mucus secretion in a subject) is obtained. The specification as filed provides no specific guidelines in this regard.

Therefore, in view of the lack of working examples of peptide inhibitors which function in vivo to inhibit mucus secretion, the breadth of the claims, the insufficient description of a representative number of peptide inhibitors or peptide stimulators, and the unpredictable behavior of peptides as observed by the opposite influences of the peptides according to SEQ ID NO: 1 and 2 on mucus section, the specification does not describe the method of inhibiting or increasing mucus secretion in a subject by the administration of peptides, in a sufficient manner

so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation.

Claim Rejections - 35 USC § 103

6. The rejection of claims 1-4, and 6 under 35 U.S.C. 103(a) as being unpatentable over Steel et al., McCool et al. and Nakamura et al. in view of Graff et al., Staddon et al. (US Patent No. 6,407,058 B1), and Ali et al, is withdrawn in response to Applicant's arguments.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1, 6-11, 14-19, 24-25, 39, 42-43, 48, 50, and 67-76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8-16, 20-27, 31-34, 37-42, and 47-51 of copending Application No. 10/180753. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are expressly claiming the same subject matter, although they differ in scope. The claims of the copending application and the claims of the instant application are both drawn to methods comprising the administration of the MANS peptide, and active fragment of the MARCKS protein. The instant claims are broadly drawn to a method for inhibiting mucus

secretion, however the scope of this method encompasses treating diseases associated with mucus secretion such as those drawn to wherein mucus secretion is an inflammatory mediator, see the claims of the copending application, particularly claims 37-42. Claims 37-42 are specifically drawn to methods for the inhibition of mucin secretion, comprising the administration of the MANS peptide. Therefore, the instant claims, wherein are directed to mucus secretion are an obvious variation of the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1635

JLE